REMARKS

I. Status of the claims

Claims 1, 3-6, and 9-25 are pending. No claim is presently amended. Claims 2, 7, and 8 were previously canceled without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications directed to canceled subject matter. Claims 6 and 10-24 are withdrawn.

II. Status of examination

Applicants acknowledge receipt of the Patent Office's advisory action dated June 22, 2005. Applicants understand that the Office has entered Applicants' claim amendments of May 25, 2005, and has withdrawn the following rejections:

(i) the rejection of claims 1-5, 8, 9, and 25 under Section 112, first paragraph for introducing allegedly new matter;

(ii) the rejection of claims 1-5, 8, 9, and 25 under Section 112, second paragraph as allegedly unclear;

(iii) the rejection of claim 25 under Section 112, first paragraph for introducing allegedly new matter;

(iv) the rejection of claims 1-5 and 9 under Section 112, first paragraph for alleged lack of written description; and

(v) the rejection of claims 1-5, 8, 9, and 25 under Section 102(b) as allegedly anticipated by Li (*Archives of Biochem.*) or Li (*Biochem. Biophy. Res.*).

The Office maintains, however, the prior rejection of claims 1, 3-5, 9 and 25 under Section 112, first paragraph as allegedly non-enabled. Applicants address this rejection in the following subsection.

III. Applicants provide data to corroborate the specification's assertion that a chimeric mouse will express all of the cytochrome genes in the CYP3A cluster of human chromosome #7 and that such expression can be induced by rifampicin

Claims 1, 3-5, 9 and 25 are rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly "fails to provide any guidance with regard to the production of other mice expressing other cytochrome [P450] family gene members and one would not be able to rely upon the state of the art to predict the resultant phenotype."

Furthermore, the Office states that claim 25 requires the expression of the human cytochrome gene to be induced by a compound but that the specification allegedly fails to teach "how many cells would have to have [the gene] ... and how much expression of those cells would be sufficient to produce the effect of expression of CYP3A4 enzyme upon administration of the substrate."

In reply, Applicants assert that (a) the human chromosome #7 fragment that is introduced into the mouse cell predictably expresses all of the disclosed CYP3A family genes, namely CYP3A4, CYP3A5, and CYP3A7; and (b) it is not essential to know how many cells in the claimed mouse need to be induced, by rifampicin for instance, in order for the mouse to be useful.

(a) The Ohshima declaration confirms Applicants' assertion that CYP3A5, and CYP3A7 in addition to CYP3A4 is expressed in cells of a chimeric mouse containing a human chromosome #7 fragment and that that expression can be induced by rifampicin in a reproducible and predictable manner

The present specification teaches that "the present invention provides a nonhuman animal that harbors at least CYP3A4, CYP3A5, and CYP3A7" (specification at page 13, line 26 to page 14, line 1). Furthermore, the specification relates that these cytochrome genes are arranged in the chromosome #7 fragment as a "cluster" and, since they "complement their respective functions" that it is "more desirable to introduce the [cytochrome] gene in a form of a whole cluster ... rather than the [specific] gene alone" (page 15, lines 14-19). Applicants confirmed the presence of all three genes in the human chromosome #7 fragment using the polymerase chain reaction and gene-specific primers. See page 65, line 20 to page 66 line 2. Applicants then confirmed that "expression of CYP3A4 was observed in the liver of rifampicin-administered chimeric mouse" (page 76, lines 24-25).

The Patent Office, however, questions whether either of the two other cytochrome genes, CYP3A5 and CYP3A7, are similarly expressed in the chimeric mouse. In reply, Applicants assert that the field of cytochrome gene expression, especially that relating to the CYP3A cluster, is well-established. Applicants did not need to provide any working examples to corroborate this well-established and predictable gene expression system. They provide, however, 26 working examples evidencing the presence of all three CYP3A genes in the mouse cell-integrated human chromosome #7 fragment and, specifically, the expression profile of CYP3A4.

Nevertheless, Applicants submit herewith the declaration by co-inventor Takeshi Ohshima, who corroborates the assertion made in the specification that the integrated chromosome #7 fragment expresses CYP3A5 and CYP3A7, and that expression of these genes, like that for CYP3A4, also can be induced by rifampicin.

Hence, Ohshima reports that, as expected, corroboratory experiments confirm that CYP3A5 and CYP3A7, just like CYP3A4, "were found to be expressed specifically in the liver and small intestine." He also conducted experiments that corroborate that "[E]xpression of CYP3A family genes was higher in the presence of rifampicin" compared to the mouse cyp3a11 homolog gene, which was not so induced. See Subsection 2 ("Results") of Exhibit A of the Ohshima declaration and Figures 1 and 2 accompanying the Experimental Data of Exhibit A. Accordingly, Applicants assert that the specification is fully enabled for CYP3A genes other than CYP3A4.

(b) Co-inventor Takeshi Ohshima confirms that the chimeric mouse of the present invention expresses all CYP3A family members and that it is unnecessary to determine how many cells express those genes in order for the mouse to be useful

Takeshi Ohshima also corroborates that induction of P450 genes is well known in the art, as evidenced by Kostrubsky *et al.*, *Drug Metab. Dispos.*, 27(8):887-94, 1999. See Exhibit B of the Ohshima declaration. Kostrubsky describes the use of human liver cell cultures to investigate the induction of cytochrome P450 genes by xenobiotics. Specifically, Kostrubsky relates that rifampicin is a "potent" inducer of CYP3A genes and is "widely used as a prototypical inducer" of CYP3A genes. See paragraph 20 of the Ohshima declaration.

Moreover, Kostrubsky says that the ability of rifampicin to maximally induce CYP3A genes makes it extremely useful "as a positive control treatment to study the induction of CYP3A." See paragraph 21 of the Ohshima declaration.

As Applicants previously attested, essentially all of the cells of the chimeric mouse produced according to the present methods will contain the human chromosome #7 fragment and, therefore, the CYP3A cluster of genes.

Accordingly, Ohshima concludes that "there is no question that researchers in this field were confident at the time when the present invention was made, (a) that it was possible to appropriately induce CYP3A gene expression and activity and (b) that such induced CYP3A activity was sufficient to study the metabolic consequences of a subsequently-administered drug." See paragraph 23 of the declaration.

For at least these reasons, Applicants assert that the specification is enabling for CYP3A5 and CYP3A7 genes in addition to CYP3A4 and respectfully request that the Office withdraws this rejection.

IV. Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date 25 July 2005

By S. A. Bent

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5404
Facsimile: (202) 672-5399

Stephen A. Bent
Attorney for Applicant
Registration No. 29,768